

sertraline tablets coated with similar carriers as the instant utilized carriers, therefore such composition is able to meet the functional limitations of the instant claims, because they are made of similar components. In addition, Examiner disagrees with Applicant in his assertion that Ranade's invention is directed toward devices. Examples 1-2 of Ranade is directed to controlled release tablets, not devices. Further Ranade clearly claims tablet dosage forms, claims 10-15. Mere allegation of non-equivalence does not overcome the prior art. Examiner inadvertently did not include claim 9 in this rejection in the Office Action filed on April 19, 2000. However, Ranade also meets the limitation of claim 9. Accordingly, claims 1, 6, 9-11, 14 stand rejected. [Page 2 of the Office Action]

Applicants traverse the rejection for the following reasons.

The basis of Applicants' traversal is that Ranade does not disclose all elements of Applicants' claim 1. The Examiner has made a rejection under 35 USC 102(b). Such a rejection requires that all of the elements of the claims rejected by the Examiner be present in Ranade. Hybritech Inc. v. Monoclonal Antibodies, Inc. 231 USPQ 81, 90 (Fed Cir 1986). Applicants' claim 1 is reproduced as follows:

A spatially delayed-release oral dosage form suitable for oral administration to a mammal, comprising sertraline or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier,

Which dosage form, following ingestion by said mammal, releases not more than 10% of the sertraline contained therein into said mammal's stomach,

And which effects immediate release of the remaining sertraline contained therein after having passed into said mammal's small intestine.

The above claim requires a device with an initial period of spatial delay, enough of a delay so that not more than 10% of the sertraline contained in the dosage form is released into the mammal's stomach. After the initial period of delay, the dosage form effects immediate release of the remaining sertraline contained therein after having passed into the mammal's small intestine. An initial period of delay is desirable, *inter alia*, so that the dosage form releases up to 90% of its contained sertraline once it has passed the mammal's upper GI tract. It is the inventors who determined that sertraline GI side effects are caused locally in the upper GI tract. It is the local mediation of GI side effects which led

the present inventors to invent a dosage form which would bypass the stomach with the great majority of contained sertraline. Until the locally mediated nature of sertraline GI side effects had been determined, there was no suggestion in the art, with any expectation of success, that a delayed release dosage form would be of any benefit.

Further, nowhere does Ranade disclose a dosage form which has an initial period of delay followed by immediate release. Ranade is a controlled release dosage form which effects sustained release, i.e., a period during which the contained therapeutic agent is released gradually and continuously (i.e., sustainedly) up until a release approaching 100% is achieved.. Any of the graphical Figures will confirm the sustained nature of the release disclosed by Ranade. No immediate release component is disclosed in a Ranade dosage form, and certainly not in conjunction with an initial delay period (Figure 7 appears to show an initial period of delay coupled with sustained release). The point is that a reference cannot anticipate an invention it does not disclose all of the elements of that invention, and the Examiner is seriously urged to reconsider the rejection on that basis. Ranade nowhere shows an initial period of delay coupled with immediate release. Accordingly, it is simply not possible for Ranade to anticipate the invention.

The Examiner appeared to be trying to rebut an argument allegedly made by Applicants in which they allegedly attempt to distinguish the instant invention over Ranade on the basis that Ranade discloses a device. Applicants were simply characterizing Ranade rather than arguing (or even asserting) that Ranade discloses devices. Applicants were not attempting to base any of their traversal on Ranade disclosing "devices", however.

Applicants do, however, disagree with the Examiner's assertion that, because Ranade discloses

"sertraline tablets coated with similar carriers as the instant utilized carriers, therefore, such composition is able to meet the functional limitations of the instant claims, because the [sic:they] are made of similar components"

The Examiner has provided no basis for the above argument. The Examiner appears to be arguing that if two dosage forms are made from or coated with similar materials, then their behavior, at least insofar as drug release is concerned, must be the same or similar. It is Applicant's position that the geometry and the structure of a dosage form, in great part, also determine the release characteristics thereof. The Examiner has provided no basis that similarity between carrier materials is controlling with respect to release characteristics.

A fair reading of Ranade makes it clear that Ranade is related to a (first order) controlled release dosage form. Ranade does not disclose a dosage form having an initial delay followed by immediate release. Accordingly, Ranade can not disclose Applicants' invention, hence cannot anticipate. Withdrawal of the rejection is accordingly respectfully requested.

Claims 1-53 stand rejected over WO 92/02212 (Herbig). The Examiner stated, in pertinent part:

Applicant argues that Herbig does not teach an initial period of delay engineered into the device which following the initial delay period, effects immediate release of the remaining active ingredient. Applicant also argues that the cellulose acetate of Herbig is used for a different purpose and thus is not a pH-sensitive structure.

In response Examiner states that the pending composition claims are solely directed to sertraline and a suitable carrier. Herbig teaches such combination. Thus, their compositions can inherently meet such functional limitations as argued by Applicant. Further, the intended use of a component such as hydroxymethylcellulose in a composition must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If prior art teaches such component, then said component is capable of performing the functional limitation thereof, in the instant case being pH-sensitive. Applicant has not met his burden of showing the difference between the prior art and the instant claimed invention. Claims 1-53 stand rejected for the reasons of record. [page 3 of the Office Action]

The Examiner argues that Applicants' claims are solely directed to sertraline and a suitable carrier. Applicants traverse the rejection on the basis that the Examiner's statement simply is not true. There are many more

elements to Applicants broadest claim than simply sertraline and a carrier. Applicants' claim 1 requires a dosage form having a spatial delay followed by immediate release. Herbig neither discloses nor suggests, anywhere, any dosage form having a delayed release component, for any drug. For that matter, Herbig's disclosure says nothing about an immediate release component as part of his claimed dosage form either. Once Herbig's core is surrounded by an asymmetric membrane (comprising a porous substructure and an IF membrane), it is a sustained release dosage form. No delay component is present. No immediate release component is present.

Parenthetically, the Examiner appeared to be making an argument based on "hydroxymethylcellulose". The argument is not understood since the word "hydroxymethylcellulose" is believed not to appear or have been used anywhere in the instant application.

Herbig discloses a pharmaceutical dosage form which exhibits sustained release, period. It comprise a core which in turn comprises an active substance surrounded by a porous substructure and one or more interfacial (IF) membranes. The porous substructure acts as a support for the IF membrane. The active substance(s) (and excipients, if any) are released from the device through the asymmetric membrane by either diffusion or osmotic pumping. Herbig neither discloses nor suggests anything relating to a dosage form having an initial period of delay engineered into the device which, following the initial delay period, effects immediate release of the remaining active ingredient. Herbig discloses a sustained release device, and discloses no component of delay or immediate release. It is not seen how Applicants' device which has a delay component and an immediate release component can be obvious over a reference which discloses neither component.

Because Herbig neither discloses nor suggests the elements which form Applicants dosage form, it is not possible for Applicants' to be obvious over Herbig. Withdrawal of the rejection is accordingly requested.

Claims 1-53 stand rejected over Bechgaard in view of Drug Facts and Comparisons (Drug Facts). The Examiner stated:

Applicant's arguments with respect to the rejection under 35 U.S.C. 103(a) as being unpatentable over Bechgaard et al EP 0080341, in view of the teachings of Drug Facts and Comparisons have been fully considered but are not found persuasive.

Applicant argues that prior to this invention the art did not disclose that sertraline side effects were locally mediated and thus could offer no expectation of success that delayed release sertraline as defined in the instant claims would treat such side effects.

In response to applicant's argument that the locally mediated side effects were not known in the art, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60(Bd. Pat. App. & Inter. 1985). As shown in the Drug Facts and Comparisons, Sertraline is associated with gastrointestinal side effects which as recognized in the art is best alleviated by enteric coating of the compound to create a delayed release dosage form. Therefore, there is motivation in the art to coat sertraline. Further, Optimizing the concentration of a coating material to facilitated disintegration at a desirable pH is well within skill level of an ordinary artisan. Accordingly, claims 1-53 stand rejected. [Pages 3-4 of Office Action]

The rejection is traversed on the basis that (1) the references cited by the Examiner neither disclose nor motivate Applicants' invention and (2) the rejection is clearly based on hindsight. Both traversals are discussed below.

With respect of point (1), the locally mediated nature of sertraline GI side effects was not known prior to the human clinical studies disclosed in the application (see Example 2). This is stated in the specification at page 2, lines 20-24. Such GI side effects are not universally locally mediated for all drugs which elicit them. For example, anti-neoplastic drugs, including 5-fluorouracil, cytarabine, methotrexate, interferon alpha-2b, and paclitaxel can be associated with severe gastrointestinal side effects such as emesis, nausea, diarrhea, and mucositis. These drugs are generally (though not always) administered other than orally such as by IV infusion, IV bolus, intramuscular, or subcutaneous, indicating that side effects can be mediated systemically, rather than locally as in the case of sertraline. Further, these drugs are almost always administered in a slow, controlled manner, as opposed to immediate or bolus dosing, yet the incidence of side effects is high. There are two separate points which need to be

appreciated here: (1) GI side effects are not always locally mediated, but may be systemically mediated instead, and (2) side effects may or may not be ameliorated by simply slowing down the rate of drug delivery. The present invention was in large part based on the inventors' determination that sertraline side effects are locally mediated, and largely in the upper GI tract, which had not heretofore been determined. Drug Facts does not disclose the locally mediated nature of sertraline GI side effects. Bechgaard does not mention sertraline at all. Applicants' point here is that Applicants' dosage forms, which are intended to alleviate side effects mediated locally in the upper GI tract, would not be obvious if it was not known where the side effects were mediated in the first place. As illustrated by the above discussion, a delayed-plus-immediate-release dosage form of sertraline would not be effective if sertraline effected its side effects systemically. The dosage form is effective because sertraline side effects are mediated locally, but the local nature of the mediation wasn't known until the instant invention.

With respect to point (2), because the art did not disclose that sertraline side effects were locally mediated, the art could offer no expectation of success that delayed release sertraline, as required by Applicants' claims, would remediate such side effects. It is only Applicants who have done that. Drug Facts does nothing to remedy this defect in the art, as noted above. It is well accepted that, even if the art appears combinable, particularly with the aid of hindsight, the art must still suggest the desirability of a modification. The mere fact that the prior art could be modified would not have made the modification obvious unless the prior art suggested the desirability of the modification. In re Gordon, 221 USPQ 1125 (Fed Cir 1984). Certainly, without a suggestion or disclosure based in the art that sertraline side effects are locally mediated, the art cited by the Examiner can not suggest the desirability of making Applicants' dosage forms with any expectation of success. The only way one of ordinary skill in the art would find the invention obvious is through the use of hindsight, but the law is emphatic that "obvious to try" is NOT the test of obviousness under 35 U.S.C. §103. American Hospital supply Corp. v. Travenol Laboratories, Inc., 223

USPQ 577, 582 (Fed. Cir. 1984). The Federal Circuit has explained the proper test:

The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out **and would have a reasonable likelihood of success**, viewed in light of the prior art. **Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure** (emphasis added).

In re Dow Chemical Co., 5 USPQ.2d 1529, 1531 (Fed. Cir. 1988); Amgen, Inc. V. Chugai Pharmaceutical Co. Ltd. 18 USPQ.2d 1016. 1022-23 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). No expectation of success can be expected for Applicants' claims since, as explained above, sertraline was not known to cause GI side effects mediated through the upper GI tract.

Further, Bechgaard teaches coatings which dissolve in the distal part of the small intestine, i.e., near the colon. See Bechgaard, page 14, first two full paragraphs. For that, Bechgaard teaches an enteric coating which is substantially insoluble at a pH below 7, i.e., below a pH which is characteristic of the lower small intestine. This is in contrast to Applicants who disclose water solubility and/or water disintegrability for their coatings at a pH above 5.0 (page 11, first three lines). By this feature, Applicants' make possible dosage forms which will disintegrate at a pH of 6 to 6.5, which pH is characteristic of the upper small intestine. Bechgaard, by means of his requirement for an enteric coating which is substantially insoluble below a pH of 7 (see Bechgaard at page 14, lines 1-4) would permit little or no release at the lower pH of upper small intestine. In this respect, one following the teachings of Bechgaard would be led away from Applicants' invention.

Further, Bechgaard teaches nothing about temporally delayed dosage forms, as claimed in Applicants' claims 27-40. The Examiner has not addressed this point, but this difference should certainly not be ignored. In re Boe et al., 184 USPQ 38 (CCPA 1974).

In view of the above arguments, it is requested that the rejection over Bechgaard in view of Drug Facts be withdrawn.

Claims 1-53 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Perry et al US Patent 6,066,643 and Bechgaard et al EP 0080341, in view of the teachings of Drug Facts, for the reasons stated in the Office Action. It is requested that this rejection be withdrawn on the basis that Perry, the primary reference, is not a reference against the instant application. It is noted that the instant application was based on PCT/IB98/00937, and that Applicants' International filing date, which is their effective US date, is 16 June 1998. It is further noted that In their combined Declaration and Power of Attorney, Applicants claimed the benefit of priority under 35 USC §119(e) to their provisional US Application No. 60/051,499 filed July 1, 1997. Applicants provisional date precedes all of Perry's relevant filing dates, including Perry's provisional application date of October 17, 1997. Applicants claim the priority of their provisional date in this matter, if necessary. In any event, since Applicants have an earlier filing date, Perry is not a reference, and the rejection must fall on that basis. Withdrawal of the rejection is accordingly respectfully requested.

Claims 1-53 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-105 of copending Application No. 09/380,897. Although the conflicting claims are not identical, they are not patentably distinct from each other because both claimed inventions are directed to delayed release sertraline dosage forms and methods of use thereof.

The rejection is traversed on the basis that the two applications are each directed to separate and distinct subject matter, each subject matter being non-obvious over the claims of the other patent. The instant application, as noted above is directed to a sertraline dosage form which operates by delaying release followed by immediately releasing its remaining sertraline. The double patenting reference, 09/380,897, is directed to a sertraline sustained release dosage form, i.e., a dosage form which meters out sertraline slowly and continuously with time. The two components of the instant invention, a delay and immediate release are each mutually independent of the mode of release in the double patenting reference, sustained release. There is no way that a device or dosage form

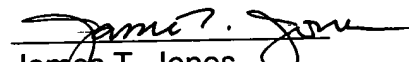


according to either invention would provide any protection to a device or dosage form of the other, and there is no way that a device according to either application would be obvious from the claims of the other. That is, a sustained release device would not be obvious from a device which effects release by a different mechanism - - a delay followed by immediate release. Similarly, a delayed release followed by immediate release would not be obvious from a device which again operates according to a different mechanism,- -sustained release.

In view of the foregoing comments and amendments, this case is believed to be in condition for allowance, and a Notice of Allowance is courteously solicited.

Respectfully submitted,

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